Sleep Medicine 59 (2019) 101–106

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Development of the Nocturia Sleep Quality Scale: a patient-reported outcome measure of sleep impact related to nocturia

Carla DeMuro Romano [a, *], Sandy Lewis [a], Amy Barrett [a], Fredrik L. Andersson [b], Valerie Williams [a], Sonia Ancoli-Israel [c], Thomas Roth [d]

[a] RTI Health Solutions, Research Triangle Park, NC, USA
[b] Ferring Pharmaceuticals, Copenhagen, Denmark
[c] University of California San Diego School of Medicine, San Diego, CA, USA
[d] Henry Ford Hospital, Detroit, MI, USA

ARTICLE INFO

Article history:
Received 17 September 2018
Received in revised form
27 January 2019
Accepted 8 February 2019
Available online 18 February 2019

Keywords:
Nocturia
Sleep impact
Patient-reported
Development
Qualitative

ABSTRACT

Background/objective: Nocturia's impact on sleep causes significant burden for patients. This study aimed to develop a novel patient-reported outcome (PRO) measure, the Nocturia Sleep Quality Scale (NSQS), for the assessment of the impact of nocturia (defined as ≥2 nocturnal voids/night) on sleep.
Methods: Sleep-related concepts were identified through a targeted literature review, after which in-depth concept elicitation interviews with patients with a clinical diagnosis of nocturia were conducted. Draft items were generated to address concepts identified as important, meaningful, and relevant. Items were further refined through three iterative sets of cognitive debriefing interviews to optimize instructions, question wording, and response options. Two sleep research experts also provided input.
Results: The literature review and data from 18 concept elicitation interviews provided the basis for a comprehensive set of concepts. Constant comparative analysis was used to identify themes and support item development. The draft questionnaire consisted of 14 items with item-specific response scales. Wording and scaling of the items was optimized based on feedback from the 22 cognitive debriefing interviews and expert input. The results confirmed the completeness and relevance of the NSQS, providing support for the content validity and ability of items to reflect patient perception of nocturia-related sleep impacts.
Conclusions: The 6-item NSQS assesses the impact of nocturia on sleep by evaluating nighttime awakenings, sleep quantity, and sleep quality. The NSQS is self-administered and is intended to assess change in nocturia's impact on sleep after treatment in a standardized manner. Psychometric evaluation is under way to describe key measurement properties.

1. Introduction

As defined by the International Continence Society, nocturia is "the complaint that the individual has to wake at night one or more times to void." [1] Therefore, clinical trial populations typically focus on patients who experience at least two or more voids per night, excluding those who experience fewer than two voids per night, as they are generally not regarded as having clinically significant nocturia. The threshold of two or more voids is suggestive of greater patient impact and warrants diagnostic investigation and treatment. Nocturia is also associated with both sleep disturbance as well as specific sleep disorders, such as sleep-disordered breathing, and depression (a condition suggested to have a bidirectional association with nocturia as well as sleep) [2–4]. Nocturia may result in reduced sleep efficiency (percentage of time in bed spent asleep) [5] and disruptions in slow-wave, restorative deep–sleep cycles that are believed to play a role in memory consolidation [6–8]. Additionally, sleep disturbance caused by nocturia has been shown to impair daytime functioning, health-related quality-of-life, and productivity in patients experiencing two or more voids per night [5]. It has also been found to be more bothersome than daytime lower urinary tract symptoms [9].

* Corresponding author. RTI Health Solutions, 200 Park Offices Drive, Research Triangle Park, NC, 27709, USA.
E-mail addresses: demuromercon@rti.org (C.D. Romano), slewis@rti.org (S. Lewis), abarrett@rti.org (A. Barrett), fredrik.andersson@ferring.com (F.L. Andersson), vwilliams@rti.org (V. Williams), sancoliisrael@ucsd.edu (S. Ancoli-Israel), TRoth1@hfhs.org (T. Roth).

https://doi.org/10.1016/j.sleep.2019.02.006
1389-9457/

The degree of bother associated with nocturia tends to increase with nocturia frequency [10]. To characterize the prevalence of nocturia, a cross-sectional survey of the adult general population in the United States, United Kingdom, and Sweden (n = 20,000) was conducted [11]. Findings from this study indicate that 69.4% of men and 75.8% of women reported experiencing at least one nocturia episode daily, and 28.5% of men and 33.7% of women reported experiencing at least two nocturia episodes daily. These results suggest that nocturia is a highly prevalent condition that poses both a significant quality-of-life–related burden as well as being related to other morbidities in the adult population [11a].

A variety of validated patient-reported instruments are available to assess sleep disturbance, including the Pittsburgh Sleep Quality Index (PSQI) [12] and the Insomnia Severity Index (ISI) [13]. Other patient-reported instruments assess sleep as part of a larger questionnaire on voiding, such as the American Urological Association (AUA) Symptom Index/International Prostate Symptom Score (AUA-SI/IPSS) [14,15] and the Nocturia, Nocturnal Enuresis, and Sleep-interruption Questionnaire (NNES-Q) [16]. However, these measures are not specific to nocturia and/or were not developed in accordance with the US Food and Drug Administration's (FDA's) guidance on the use of patient-reported outcome (PRO) measures in support of product approval and labeling [17]. Thus, the objective of this study was to develop a novel PRO measure, the Nocturia Sleep Quality Scale (NSQS), to capture the nocturia-specific impact on patients' sleep and to provide a patient-centered framework to evaluate treatment benefits with current and emerging nocturia treatments.

2. Methods

Development of the NSQS was consistent with the FDA PRO guidance [17,18] in that it was informed by a literature review to identify concepts relevant to patients' experiences with nocturia and its impact on sleep, concept elicitation interviews with patients, item generation and development of a conceptual framework, cognitive debriefing interviews with patients, and consultation with clinical experts.

2.1. Literature review

The search strategy identified 95 articles including terms related to nocturia and sleep disturbance. After review of the citations and abstracts, 34 articles focusing on the following topics were selected for further review:

- Patient experience of nocturia
- Impact of nocturia on sleep
- Treatment of nocturia (clinical trial or interventional observational studies) that included or appeared to include PRO measures related to nocturia
- Development or evaluation of a PRO measure assessing nocturia or sleep disturbance in a nocturia patient sample

Nine of these articles were subsequently excluded from full-text review because they duplicated study results, did not include relevant results, or did not focus on the population of interest. A total of 25 papers were selected based on the topics noted above. As this was not a systematic search but a targeted review, other papers were eliminated as described. Details from the 25 included articles, as well as the additional resources identified through subsearches and review of article references, are provided in the following sections.

2.2. Concept elicitation

To elicit patient-reported concepts important to patients with nocturia, two rounds of individual, in-depth concept elicitation interviews were conducted with a total of 18 patients at qualitative research facilities in Chalfont, Pennsylvania, and Raleigh, North Carolina. Eligible participants recruited through a qualitative research facility were required to have experienced nocturia (≥2 nocturnal voids per night) for six months or longer, all or almost all nights during the past two weeks; had moderate to extreme self-reported sleep disturbance due to nocturia during the past two weeks; and were able to understand written and spoken English. Exclusion criteria were applied to avoid inclusion of participants with confounding sleep conditions.

Three highly experienced interviewers (S.L., C.R., and A.B.) conducted each interview. Participants were given an overview of the study and were asked to provide written informed consent at the beginning of each interview. A semistructured interview guide was used to standardize the interviews. Interviews began with open-ended questions to elicit participants' experiences with nocturia, focusing on the impact on sleep. Follow-up questions explored concepts identified in the literature with each participant and the types or level of improvement in nocturia that would make a meaningful difference to the participant in terms of his or her sleep. All interviews were audio recorded and transcribed. The study was approved by the RTI International institutional review board, independent of RTI Health Solutions.

A continuous comparative analysis [19] of the data collected was conducted using the transcripts and detailed field notes collected during the interviews. Dominant themes within each interview were identified and compared across the results of other interviews to generate themes or patterns in the ways participants described their experiences. Concept saturation was documented using a saturation grid. As noted individual interviews were compared to assess saturation.

2.3. Development of the items

Results from the concept elicitation interviews were compiled to identify the emergent themes and concepts within the data to support item generation. To guide the development of item wording, patient language was examined to understand how these concepts were experienced and described by patients, and items were derived based on a prespecified set of ground rules consistent with standard qualitative research techniques to focus item creation. Decisions regarding concepts for inclusion in the new measure took into account various criteria, including the frequency and importance of concepts, terminology with which concepts were reported by interview participants, support of the concepts from the literature and existing PRO measures, the opinions of clinical experts, and feasibility of assessment via self-report. These criteria were not prioritized.

2.4. Cognitive debriefing

Three iterative rounds of cognitive debriefing interviews were conducted with a total of 22 additional patients with nocturia. The eligibility criteria and recruitment procedures were similar to those used during the concept elicitation interviews. The interviews were held in qualitative research facilities in Chalfont, Pennsylvania, and Raleigh, North Carolina.

The same interviewers who led the concept elicitation interviews used a standard “think-aloud” procedure and directed probes to delve further into the question-answering process. Specifically, participants were asked to respond to the draft NSQS items while describing their thought processes out loud. Targeted probes were also asked to elicit further information about the way participants interpreted the items (in the participants' own words) and their thoughts about the response options. To gather information about the feasibility and usability of an electronic smartphone

platform, draft questionnaire items were also tested with the same participants on an electronic device.

A conceptual framework for the NSQS, describing the expected relationships of items within a domain and expected relationships among domains, was developed [20]. The conceptual framework was drafted based on dominant themes noted in the literature and patient input from the concept elicitation interviews and then was refined through additional patient input during cognitive debriefing interviews and consultation with clinical experts.

2.5. Expert review

During development of the NSQS, the draft version of the instrument was reviewed and critically examined by two experts in the field of sleep research, specifically disturbed sleep (T.R. and S.A-I.).

3. Results

3.1. Literature review

On the basis of the literature reviewed, patients with nocturia experience disturbed sleep caused by frequent awakenings to void [7,21–27], difficulty falling back to sleep after waking [27,28], bother related to the need to void during the night [23,28], insufficient sleep or insufficient restorative sleep [7,23,25,27,28], and premature waking in order to void [7,22,25,29,30].

3.2. Concept elicitation

Concept elicitation interviews built on the findings from the literature review, with the goal of exploring and confirming the concepts most relevant to measuring the impact of nocturia on sleep. Of the 18 participants, 50% were female and 83.3% had at least some college or an associate degree; 55.6% were employed either part or full time (Table 1). Eleven participants (61.1%) reported being "quite a bit disturbed" by nocturia-related sleep disturbance, and seven (38.9%) reported being "moderately disturbed."

All 18 participants reported multiple awakenings each night to urinate, some with a consistent pattern of sleeping and waking. Others had a wider range in the number of awakenings and could discern no reason for awakening to urinate more or less some nights compared to others. For example, these participants could not link these events to fluid intake or bedtime.

The primary impacts of nocturia were identified as awakening frequently during the night to urinate and the impact on overall sleep quantity and quality caused by these awakenings. Specifically, with respect to frequent awakenings, one participant noted that "[a]t night, even though I'm [a] heavy sleeper, I felt very uncomfortable, and I was starting to get up one or two times extra at night …. I cut back on the water drinking, but I'm still getting up two or three times." Another participant recalled having awakened "probably four or five times a night for the last three or four years." Participants also indicated that their frequent awakenings interfered with the quality and restfulness of their sleep, indicating, for example, "I mean, I'm sleeping, but it's not good quality because I get woken up so I don't get the deep sleep" and "I don't get a fulfilled night's sleep if I'm up multiple times." Importantly, these awakenings were independent of the number of actual voids. Participants described being awakened by the need to void but also described postponing the actual void at times and attempts to go back to sleep without voiding.

Table 2 presents a list of concepts identified in the interviews that were considered for possible inclusion in the NSQS. Concept saturation was determined to be achieved across the overall sample of 18 participants, and therefore the recruitment sample was deemed sufficient. Specifically, no new concepts were identified in

Table 1
Characteristics of concept elicitation and cognitive debriefing interview participants.

Demographic Information	N (%)
Concept elicitation interview participants	n = 18
Sex	
Female	9 (50%)
Male	9 (50%)
Age (years)	
Mean	56.3
Range	28–87
Race	
White	16 (88.9%)
African American	2 (11.1%)
Education	
High school/GED	3 (16.7%)
Some college/associate degree	7 (38.9%)
College degree	2 (11.1%)
Professional or advanced degree	6 (33.3%)
Employment[a]	
Employed full time	8 (44.4%)
Employed part time	2 (11.1%)
Not employed/retired	8 (44.4%)
Number of voids per night in past two weeks	
Two times	9 (50.0%)
Three times	6 (33.3%)
Four or more times	3 (16.7%)
Sleep disturbance related to nocturia in past two weeks	
Moderately disturbed	7 (38.9%)
Quite a bit disturbed	11 (61.1%)
Extremely disturbed	0 (0%)
Length of time nocturia experienced (years)	
Mean	4.1
Range	2–15
Diagnosed conditions that may affect polyuria	
Enlarged prostate gland (males only)	4 (22.2%)
Overactive bladder	3 (16.7%)
Cognitive debriefing interview participants	n = 22
Sex	
Female	11 (50%)
Male	11 (50%)
Age (years)	
Mean	56.9
Range	32–73
Race/ethnicity[a]	
White	18 (81.8%)
African American	1 (4.5%)
Asian	1 (4.5%)
Hispanic	1 (4.5%)
Other	1 (4.5%)
Education[a]	
High school/GED	2 (9.1%)
Some college/associate degree	8 (36.4%)
College degree	8 (36.4%)
Professional or advanced degree	4 (18.2%)
Employment	
Employed full time	11 (50.0%)
Employed part time	2 (9.1%)
Not employed/retired	9 (40.9%)
Number of voids per night in past two weeks	
Two times	15 (68.2%)
Three times	3 (13.6%)
Four or more times	4 (18.2%)
Sleep disturbance related to nocturia in past two weeks	
Moderately disturbed	7 (31.8%)
Quite a bit disturbed	13 (59.1%)
Extremely disturbed	2 (9.1%)
Length of time nocturia experienced (years)	
Mean	4.4
Range	<1-10
Diagnosed conditions that may affect polyuria	
Enlarged prostate gland (males only)	3 (13.6%)
Overactive bladder	2 (9.1%)

[a] Percentages do not add up to 100 due to rounding.

Table 2
Concept elicitation summary from participants with disturbed sleep related to nocturia (N = 18).

Concept	Participants																		Total
	Round one										Round two								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	
Experiencing frequent awakenings	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	**18**
Awakened by sensation of needing to urinate	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	—	✓	✓	✓	—	**16**
Feeling tired during the day	✓	✓	✓	✓	✓	—	✓	✓	✓	✓	X	✓	✓	—	✓	✓	✓	✓	**15**
Having reduced sleep quality	✓	—	✓	✓	✓	X	✓	✓	✓	✓	✓	✓	✓	X	—	✓	X	✓	**13**
Feeling bothered by frequent awakenings	—	✓	✓	✓	✓	✓	✓	✓	✓	✓	—	—	—	✓	—	—	—	✓	**11**
Having short blocks of uninterrupted sleep	✓	✓	✓	✓	✓	—	—	✓	✓	✓	—	✓	✓	X	X	X	—	✓	**11**
Having consistent pattern of awakenings	✓	✓	✓	✓	✓	✓	—	✓	X	X	–	✓	—	—	✓	✓	—	X	**10**
Having reduced overall sleep time	—	—	—	✓	—	—	—	✓	✓	✓	X	✓	✓	—	✓	✓	X	✓	**9**
Not experiencing restful/restorative/deep sleep	—	✓	✓	✓	—	X	✓	✓	✓	—	—	✓	✓	X	—	✓	—	—	**9**
Difficulty going back to sleep after getting up to urinate	✓	X	✓	✓	—	X	✓	✓	—	—	✓	✓	X	—	X	—	✓	✓	**9**
Napping during the day	—	—	✓	–	✓	—	✓	—	X	✓	✓	X	X	—	✓	✓	X	X	**7**
Waking for the day before the intended time	✓	—	—	—	—	✓	—	—	—	✓	—	✓	✓	—	—	—	✓	✓	**7**
Feeling moody, irritable, or having difficulty focusing during the day	—	—	✓	—	—	✓	—	—	—	✓	—	—	✓	—	—	—	—	—	**4**
Avoiding activities involving sleeping away from home	—	–	✓	—	✓	X	✓	X	X	—	X	X	✓	—	X	—	X	X	**4**

✓ = reported by participant; X = not a problem or issue for participant; — = not discussed.

the second round of concept elicitation interviews. Concepts were deemed relevant and appropriate for consideration across all nocturia severity levels.

3.3. Development of the items and draft conceptual framework

A preliminary list of 14 items employing potential item-specific response scales (varied verbal response scales and 6-point and 11-point numerical rating scale options) and a recall period of "from the time you went to bed, with the intention to sleep, until you woke up to start your day" was developed for initial evaluation in round one of the cognitive debriefing interviews. A preliminary conceptual framework for the NSQS was also developed and while not directly reviewed by interview participants, the framework was refined based on the results of the cognitive debriefing interviews and expert review (Fig. 1).

3.4. Cognitive debriefing

Of the 22 cognitive debriefing interview participants, 50% were female and 90.9% had at least some college or an associate degree; 59.1% were employed either part or full time (Table 1). In general, all participants across the three rounds of interviews reported that the draft items were clear and easy to answer.

Item alternates to assess the number of awakenings due to the need to urinate were initially tested in round one. Participants found the option "How many times did you wake last night due to the need to urinate?" to most clearly capture the concept of nighttime awakenings due to the need to urinate. This item was subsequently tested in rounds two and three. Participants across all three rounds of testing found the item important and relevant. During testing, participants were probed on the clinical meaningfulness of change in this item. Some participants noted that symptoms would need to "go away completely." Others remarked that a reduction in the overall number of awakenings would be meaningful in terms of treatment benefit, with many reporting that reduction by half would signify a meaningful benefit. Participants described the impact of frequent awakenings from sleep and the lack of any significant blocks of deep, uninterrupted sleep and the downstream effect this appeared to have on overall sleep quality:

> *"I feel like maybe I didn't get as much sleep as I possibly could have because my sleep's interrupted. I didn't get that comfortable relaxation."*

> *"I wish I didn't get up. You feel like you're robbed."*

> *"Because the first couple of hours are really the only hours [of good quality sleep] and then maybe from 5:00 to 6:00 [a.m.]. So the sleep in between is not deep sleep. I can't fall asleep, and I just feel like I am tossing and turning, and I can't get settled."*

> *"I think the first part of it [the night] is way better than the second part. Once I get interrupted then you're trying to fight back to sleep, or you can toss and turn."*

> *"I mean, I'm sleeping, but it's not good quality because I get woken up so I don't get the deep sleep."*

> *"I don't get a fulfilled night's sleep if I'm up multiple times."*

Two concepts were included in the hypothesized domain of sleep quantity: total sleep duration and early awakening. Of the item alternates to assess total sleep initially tested during round one, participants found the option "Thinking over the entire night, how much time (in total) were you awake because you needed to urinate?" to most clearly capture the concept of interruption or reduction in total sleep duration due to the need to urinate. Item alternates to assess early awakening were initially tested during round one, and the preferred option was refined during round two. In round three, the option "How much earlier than planned did you get up for the day because you were awakened by the need to urinate?" was tested and endorsed by participants. Participants across all three rounds of testing found the items evaluating total sleep duration and early awakenings to be important and relevant.

Three concepts were included in the hypothesized domain of sleep quality: overall, restful sleep, and refreshing sleep. Item alternates to assess overall sleep quality were initially tested during round one, and the preferred option was refined during round two. In round three, the option "How would you rate the overall quality of your sleep last night due to being awakened to urinate?" was tested and endorsed by participants. Two item alternates to assess restful sleep were initially tested during round one: "How restful or restorative was your sleep … ?" and "How tired did you feel when you got up this morning … ?" Upon review of the item alternates for restful sleep presented during round one, participants found that the alternates captured unique aspects of the overall concept. While restful sleep captured the degree of lack of interruption in sleep, assessment of tiredness in the morning coincided more with the perceived ability to accomplish daily activities. Because the

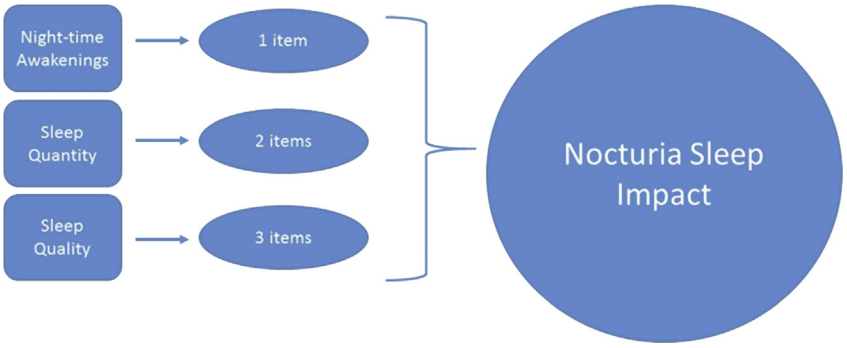

Fig. 1. Conceptual framework of Nocturia Sleep Quality Scale—Final developmental version.

word restorative was deemed to be higher-level vocabulary, the item was simplified to ask only "How restful was your sleep?" Finally, a single item to assess refreshing sleep was tested during the first and second rounds of interviews. Upon review of the item, participants found a close association with refreshing sleep and restful sleep and indicated that restful sleep and overall sleep quality better captured the concepts of importance. Therefore, this item was not retained for further evaluation in round three.

The recall period of "from the time you went to bed, with the intention to sleep, until you woke up to start your day" was tested in all three rounds of interviews. Participants found the recall period to be clear and easy to consider when responding to the items. In addition, the recommended instructions for respondents advise completion of the tool in the morning, after the individual has awakened to start the day to limit recall bias.

The draft NSQS was formatted for a smartphone platform and piloted with round one cognitive debriefing interview participants ($n = 7$). Overall, participants were receptive to using an electronic device to complete the questionnaire and were able to read and respond to the items presented on the smartphone.

3.5. Expert review

Based on the recommendations of clinical experts, selected items and response options were refined. Specifically, the response options for the items about total sleep and early awakening were aligned, and the phrase "Considering the number of times you were awakened to urinate" was added to both the restful sleep and tiredness items. The refined instrument was well received and endorsed by the clinical experts.

3.6. Final concepts included in the NSQS

The following concepts are included in the developmental version of the NSQS, reflecting refinements made based on input from patients and clinical experts:

1. Waking due to the need to urinate
2. Time awake due to need to urinate
3. Early awakening
4. Restfulness of sleep
5. Tiredness
6. Sleep quality

4. Discussion

The NSQS is a brief, patient-reported measure designed to assess the impact of nocturia on sleep. The tool is designed for use in a clinical trial setting and was developed in full alignment with the FDA PRO guidance [17]. The developmental version of the tool consists of six items assessing hypothesized domains of number of nighttime awakenings, sleep quantity, and sleep quality. These items are designed to be both gender and culturally neutral (appropriate for cultures outside of the US). The NSQS employs a short recall period of "from the time you went to bed, with the intention to sleep, until you woke up to start your day" to allow patients to assess the impact of nocturia on sleep over time. As noted, the new tool is designed to be self-administered, gathering direct patient input without the influence of others, and is intended to assess change after treatment in a standardized manner. The results of the literature and instrument review combined with data collected from the 18 concept elicitation interviews provided the basis for identifying a comprehensive set of concepts to assess the impact of nocturia on sleep.

The experience of nocturia has a profound impact on sleep quality. This observation was supported not only through a review of the literature and expert input but also by patient direct report. Awakenings due to nocturia were described as independent of the number of actual voids per night and could more accurately describe the impact of nocturia on sleep quality. Notably, interview participants were able to accurately describe experiences related to the night before and reflect easily on a 24-h or even greater time period noting change or differences over time. Interview participants also clearly articulated thoughts in regard to meaningful change in nocturia-related nighttime awakenings. Ideal improvement was expressed as complete elimination of nighttime awakenings due to nocturia; however, most indicated that an approximate 50% reduction in the number of awakenings would be very meaningful to them in terms of treatment benefit. For example, if the participant was experiencing two nighttime awakenings, a reduction to just a single awakening would be viewed as beneficial from a patient's perspective and efficacious in the case of a therapeutic intervention. Participants described the importance of uninterrupted blocks of sleep and the impact of these uninterrupted periods on sleep quality as highly relevant.

Given this level of burden, combined with the demonstrated ability of patients with nocturia to self-report, assessment of patient-reported sleep quality may be an important treatment benefit worthy of measure in a clinical trial setting. However, to date, no such fit-for-purpose, disease-specific tool has been available.

The NSQS items were refined through the conduct of 22 cognitive debriefing interviews with an independent sample of participants and with input from two clinical experts. Results of the cognitive debriefing interviews further support the content validity of the items and the ability of items to accurately reflect patient perception of improvement in nocturia-related sleep impacts.

A rigorous psychometric evaluation of the new NSQS is planned to provide support for key measurement properties, including the scale's reliability, validity, and ability to detect change as well as

provide an opportunity to explore meaningful change thresholds. In addition, exit interviews are planned with trial participants to extend and facilitate interpretation of the data collected using the NSQS and larger PRO battery included within the study to more fully characterize treatment benefit.

The NSQS is an especially novel tool in that it is the only measure of its kind that specifically addresses nocturia-related impacts on sleep and has been developed in alignment with FDA PRO guidance to support product approval and labeling. As such, the NSQS provides a best-fit approach to characterize nocturia-specific impacts on sleep in clinical trials. Inclusion of the NSQS with other complementary measures such as a symptom diary or other broader assessment of health-related quality-of-life will help to fully characterize treatment benefit for current and emerging nocturia treatments.

5. Limitations

This tool was developed utilizing a US-based set of interview participants. Despite the goal of creating items to be intentionally culturally generic, the tool will require cross-cultural validation for non-English versions of the measure. Additionally, while the goal was to set the tool at a fairly low reading level, the interview participants all had at least a high school education with approximately 60% with a college education. As such, study administrators should employ appropriate training methods to confirm participant ability to self-complete.

Funding

This study was funded by Ferring Pharmaceuticals. Authors from Ferring Pharmaceuticals participated in designing the study, in analyzing and interpreting the data, in writing the manuscript, and in the decision to submit the article for publication.

Acknowledgments

Medical writing services were provided by Kate Lothman of RTI Health Solutions and were funded by Ferring Pharmaceuticals, Denmark.

Conflict of interest

The study was performed under a research contract between RTI Health Solutions and Ferring Pharmaceuticals and was funded by Ferring Pharmaceuticals. S.L., C.R., A.B., and V.W. are salaried employees of RTI Health Solutions. F.A. is a salaried employee of Ferring Pharmaceuticals. S.A-I. and T.R. have both provided consultancy work for Ferring Pharmaceuticals as well as other pharmaceutical companies.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: https://doi.org/10.1016/j.sleep.2019.02.006.

References

[1] van Kerrebroeck P, Abrams P, Chaikin D, et al. Standardisation sub-committee of the international continence society. The standardisation of terminology in nocturia: report from the standardisation sub-committee of the international continence society. Neurourol Urodyn 2002;21(2):179–83.
[2] Endeshaw YW, Johnson TM, Kutner MH, et al. Sleep-disordered breathing and nocturia in older adults. J Am Geriatr Soc 2004;52:957–60.
[3] Umlauf MG, Chasens ER, Greevy RA, et al. Obstructive sleep apnea, nocturia and polyuria in older adults. Sleep 2004 Feb 1;27(1):139–44.
[4] Breyer BN, Shindel AW, Erickson BA, et al. The association of depression, anxiety and nocturia: a systematic review. J Urol 2013 Sep;190(3):953–7.
[5] Ancoli-Israel S, Bliwise D, Peter Nørgaard J. The effect of nocturia on sleep. Sleep Med Rev 2011 April;15(2):91–7.
[6] Walker MP. The role of slow wave sleep in memory processing. J Clin Sleep Med 2009 Apr 15;5(Suppl. 2):S20–6.
[7] Bliwise DL, Dijk DJ, Juul KV. Nocturia is associated with loss of deep sleep independently from sleep apnea. Neurourol Urodyn 2015 Apr;34(4):392.
[8] Holm-Larsen T, Albei C, Andersson F, et al. "My sleep pattern is a series of naps": subjective patient-reported data about what is most bothersome about nocturia. Eur Urol Suppl 2013;12:e405.
[9] Everaert K, Anderson P, Wood R, et al. Nocturia is more bothersome than daytime LUTS: results from an observational, real-life practice database including 8659 European and American LUTS patients. Int J Clin Pract 2018;72:e13091.
[10] Tikkinen KA, Johnson TM, Tammela TL, et al. Nocturia frequency, bother, and quality of life: how often is too often? A population-based study in Finland. Eur Urol 2010 Mar;57(3):488–96.
[11] Coyne KS, Sexton CC, Thompson CL, et al. The prevalence of lower urinary tract symptoms (LUTS) in the USA, the UK and Sweden: results from the Epidemiology of LUTS (EpiLUTS) study. BJU Int 2009;104:352–60.
[11a] Coyne KS, Zhou Z, Bhattacharyya SK, et al. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 2003;92(9):948–54.
[12] Buysse DJ, Reynolds CF, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989 May;28(2):193–213.
[13] Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med 2001 Jul;2(4):297–307.
[14] Barry MJ, Fowler FJ Jr, O'Leary MP, et al. The American Urological Association symptom index for benign prostatic hyperplasia. Measurement Committee of the American Urological Association. J Urol 1992;148:1549–57.
[15] Rhodes PR, Krogh RH, Bruskewitz RC. Impact of drug therapy on benign prostatic hyperplasia-specific quality of life. Urology 1999;53:1090–8.
[16] Bing MH, Moller LA, Jennum P, et al. Prevalence and bother of nocturia, and causes of sleep interruption in a Danish population of men and women aged 60-80 years. BJU Int 2006 Sep;98(3):599–604.
[17] Food and Drug Administration (FDA). Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. Available at: http://www.fda.gov/downloads/Drugs/GuidanceCompliance/Guidances/UCM193282.pdf. [Accessed 15 July 2016].
[18] Patrick DL, Burke LB, Gwaltney CJ, et al. Content validity - establishing and reporting the evidence in newly-developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO good research practices task force report: Part 1 - eliciting concepts for a new PRO instrument. Value Health 2011;14:967–77.
[19] Boeije HA. Purposeful approach to the constant comparative method in the analysis of qualitative interviews. Qual Quantity 2002;36:391–409.
[20] Donatti C, Wild D, Hareendran A. The use of conceptual models, conceptual frameworks, and endpoint models to support label claims of treatment benefit using patient reported outcomes. ISPOR Connect 2008:9–12.
[21] Berges R, Hofner K, Gedamke M, et al. Impact of desmopressin on nocturia due to nocturnal polyuria in men with lower urinary tract symptoms suggestive of benign prostatic hyperplasia (LUTS/BPH). World J Urol 2014;32(5):1163–70.
[22] Goldberg H, Baniel J, Mano R, et al. Low-dose oral desmopressin for treatment of nocturia and nocturnal enuresis in patients after radical cystectomy and orthotopic urinary diversion. BJU Int 2014;114(5):727–32.
[23] Kim SO, Choi HS, Kwon D. The alpha1 adrenoceptor antagonist tamsulosin for the treatment of voiding symptoms improves nocturia and sleep quality in women. Urol J 2014;11(3):1636–41.
[24] Simaioforidis V, Papatsoris AG, Chrisofos M, et al. Tamsulosin versus transurethral resection of the prostate: effect on nocturia as a result of benign prostatic hyperplasia. Int J Urol 2011 Mar;18(3):243–8.
[25] van Kerrebroeck P, Rezapour M, Cortesse A, et al. Desmopressin in the treatment of nocturia: a double-blind, placebo-controlled study. Eur Urol 2007;52(1):221–9.
[26] Fujimura T, Yamada Y, Sugihara T, et al. Nocturia in men is a chaotic condition dominated by nocturnal polyuria. Int J Urol 2015;22(5):496–501.
[27] Obayashi K, Saeki K, Kurumatani N. Quantitative association between nocturnal voiding frequency and objective sleep quality in the general elderly population: the HEIJO-KYO cohort. Sleep Med 2015;16(5):577–82.
[28] Vaughan CP, Eisenstein R, Bliwise DL, et al. Self-rated sleep characteristics and bother from nocturia. Int J Clin Pract 2012;66(4):369–73.
[29] Tyagi S, Resnick NM, Perera S, et al. Behavioral treatment of chronic insomnia in older adults: does nocturia matter? Sleep 2014;37(4):681–7.
[30] Yokoyama O, Hiro S, Hotta S, et al. Efficacy of fesoterodine on nocturia and quality of sleep in Asian patients with overactive bladder. Urology 2014;83(4):750–5.